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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,374	06/08/2001	Jeffrey C. Rapp	AVI-007N	2448

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AVIGENICS, INC.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,374	RAPP, JEFFREY C.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-29 and 62-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7, 9-29, 62-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 6/13/06, has been entered. No claim is amended. Claims 1-5, 7, 9-29, 62-72 are pending.

Applicant's request for continued examination is found to be persuasive and the finality of the Final Office action, mailed 4/5/06, is withdrawn. A new ground of rejection appears below.

Response to Arguments

The prior rejection of claims 1-5, 7, 9-17, 19-29, 62 and 63, under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Michael *et al.* (cited in the final Office action, mailed 4/5/06) is withdrawn.

The prior rejection of claims 64-72, under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Michael *et al.* as applied to claims 1-5, 7, 9-17, 19-29, 62 and 63 above, and further in view of Ling *et al.* (cited in the final Office action, mailed 4/5/06), is withdrawn.

The prior rejection of claims 1-5, 7, 9-29, 62 and 63, under 35 U.S.C. 103(a) as being unpatentable over Ditullio *et al.* when taken with Mohammed *et al.* (cited in the final Office action, mailed 4/5/06), is withdrawn.

Applicants' Arguments. Applicants argue that the blastodermal and ovum cell that are taught by Ditullio is not generated from the oviduct, and that the oviduct is a long tube that the yolk passes as it is packaged into a hard shell egg. The ovum, which may give rise to blastodermal cells, is the female gamete released from the ovary. Applicants have provided Figure 5-1 (Ed. By Bell) which shows the ovary and oviduct of a chicken.

Response to Arguments. These arguments, in conjunction with the Figure provided by Applicants, have overcome the art rejections of record, because the Examiner agrees that blastodermal and ovum cells are not oviduct cells.

Claim Objections

Claim 71 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recites that the avian cell of claim 64 is an oviduct cell. However, claim 64 recites an avian oviduct cell, thus claim 71 fails to further limit claim 64.

Claim 10 is objected to because of the following informalities: the claim recites variants "hereof" in the line. It appears that Applicants intended to recite thereof. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 9-29, 62-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new ground of rejection.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The claimed invention is directed to methods of producing a heterologous antibody comprising culturing an avian oviduct cell transfected with at least one expression vector comprising a nucleotide sequence encoding an immunoglobulin polypeptide under conditions to allow for the expression of the nucleotide sequence, and the production of an immunoglobulin polypeptide that forms an antibody that selectively binds an antigen, or an immunoglobulin polypeptide, that when isolated and combined with a light chain or heavy chain, forms an antibody that selectively binds an antigen, isolating the immunoglobulin produced by the cultured cells to produce the heterologous antibody. Specific embodiments limit the immunoglobulin polypeptide, and further limit the expression vector. Other embodiments are directed to avian cells from various birds. The only contemplated intended use of the claimed culture system is for use as a bioreactor to produce antibodies.

The specification teaches that the purification of monoclonal antibodies, specific for a single epitope is not feasible because the concentration of any one antibody species in serum is so low. The specification teaches that hybridomas cell lines were developed to produce monoclonal antibodies (p. 1, lines 13-19). With regard to the instantly-claimed invention, the specification teaches a working example of the transfection of quail oviduct cells, with cDNA vectors coding for either the heavy chain or light chain of a human monoclonal antibody against CTLA-4. The specification then teaches that the medium was then harvested and centrifuged, and the supernatant was analyzed for antibody content, and it showed that only cells co-transfected with both the heavy and light chain vectors expressed monoclonal antibody detectable by ELISA, but below detectable limits for FACS. See Example 1. The other working examples in the specification are not directed to the transfection of any avian oviduct cells to produce antibodies.

The specification teaches that an art-recognized problem in the production of monoclonal antibodies is the low yield of antibodies (see p. 2, lines 17-19; pages 2-3 , bridging sentence). The specification contemplates using transgenic animals in

order to express heterologous antibodies, particularly using the avian reproductive system to overcome this problem (p. 5, lines 7-9). They teach that the hen oviduct can be used as a potential protein bioreactor, particularly in the context of transgenic chickens. See page 5, lines 15-21. The specification teaches that a transfected avian cell, cultured *in vitro* can then be transferred to a fertilized, enucleated cell in methods of nuclear transfer (p. 11, lines 1-5). Thus, the only contemplated use of the claimed invention is a method to produce antibodies in an *in vivo* context. The specification is not enabled for the claimed method to produce a heterologous antibody *in vitro*, as instantly claimed, because the specification does not contemplate using a culture of transfected avian oviduct cells *in vitro* for producing antibodies. The specification's only contemplated use for the transfected oviduct cells is in the context of producing a bird that would then produce eggs that express the heterologous antibody.

The claimed invention is not enabling because of the following:

1. The specification does not teach the method step of isolating the immunoglobulin, as instantly claimed.

2. The specification does not contemplate using the claimed method in any of the uses contemplated by the specification, other than for the production of transgenic bird. It is emphasized that the specification discusses the art-recognized problems with producing monoclonal antibodies (see p. 2, lines 17-19; pages 2-3, bridging sentence). The specification does not provide a method to overcome this problem by using the instantly-claimed method of using a culture of transfected oviduct cells *inv vitro* to produce antibodies. Thus, it is unclear, from the teachings in the specification, how the skilled artisan would have used the cultured oviduct cells as a bioreactor to produce antibodies *in vitro.*

3. The specification clearly teaches that the production of antibodies, using the quail oviduct cells was only detected by ELISA, but below detectable limits for FACS. Thus, one of skill in the art, given the instant teachings could not

use the claimed invention to overcome the art-recognized problems of low antibody yield. Further, one of skill in the art could not predictably isolate the immunoglobulin produced by the claimed methods, as the yield is extremely low. For example, Kohler and Milstein (**Nature**, 256:495-497, August 7, 1975) teach the production of antibodies using hybridomas cells, and addressed the art-recognized problem of producing antibodies *in vitro*. The teach that, "The manufacture of predefined specific antibodies by means of permanent tissue culture is of general interest. There are at present a considerable number of permanent cultures of myeloma cells and screening procedures have been used to reveal antibody activity in some of them. This, however, is not a satisfactory source of monoclonal antibodies of predefined specificity." See p. 495, 1st paragraph. Thus, it is clear that the art recognizes that the production of hybridomas overcame the problem of low antibody yield. However, the instant invention fails to address this art-recognized problem because the working example in the specification clearly show that the antibody yield for the claimed invention is very low.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the claimed *in vitro* method of producing heterologous antibodies in an avian oviduct cell, the specification's teachings of very low yield to antibody when practicing the claimed method, the lack of guidance as to how to overcome the art-recognized difficulties in producing high yields of antibodies, the lack of an enabled use for the claimed method other than in the context of producing a transgenic bird, it would have required one of skill in the art to practice undue experimentation to practice the claimed method.

Written Description

Claims 1-5, 7, 9-29, 62-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification provides sufficient description for the various viral vectors recited in claim 10, but not "variants" of these vectors. Furthermore, the specification provides sufficient description of an immunoglobulin heavy chain variable region, but not a "variant thereof"; and similarly, the specification provides sufficient description for an immunoglobulin light variable region, but not a "variant thereof," as recited in claim 21. The specification fails to provide sufficient guidance for the above-recited limitations, as presently claimed, with particularity to indicate that Applicants have possession of the claimed invention. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient and relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person of skill in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48USPQ2d 1641, 1646 (1998).

In the instant case, variants of the viral vectors, heavy chain variable region or light variable region, lack a written description. The specification fails to

describe what variants would fall into this genus, when used as claimed. The specification fails to provide sufficient teachings with regard to how variable any variant must be to still be considered a "variant". For example, no core structure or guidance is given to deduce what a variant of a viral vector, a heavy chain or light chain variable region would be. The skilled artisan could not envision the detailed chemical structure of all these variant that are encompassed by the claims. Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 25, 28, 64-72 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is unclear. The claim recites that the avian cell of claim 1 is an oviduct cell or an embryonic cell. However, claim 1 specifically recites using an oviduct cell, thus, it is unclear how this cell could be an embryonic cell, or how an embryonic cell would further limit the oviduct cell. Appropriate correction is requested.

Claim 13 is unclear. It recites the method of claim, wherein "transcriptional promoter..." Claim 12 recites a constitutively active promoter, thus, it is unclear if the transcriptional promoter refers to the constitutively active promoter. Clarification and/or amendment to the claim is requested.

Claim 25 recites the limitation "the mammal" and the "avian" in lines 1 and 3. There is insufficient antecedent basis for this limitation in the claim. The claim refers back to claim 34, which is directed to a mammalian immunoglobulin polypeptide or an avian immunoglobulin heavy chain polypeptide, the claim is not directed to a mammal or avian.

Claim 28 recites the limitation "the mammal" in line 2. There is insufficient antecedent basis for this limitation in the claim. The claim refers to claim 26, which is directed to a mammalian or avian immunoglobulin light chain polypeptide, it is not directed to a mammal. Appropriate correction is requested.

Claim 64 is unclear for the following reasons: the claim recites culturing "the avian cell" under conditions wherein the nucleotide sequence is expressed. The only avian cell recite in the claim is an oviduct cell, therefore, for clarity the claim should recite "culturing the avian oviduct cell". Furthermore the claim is incomplete because it recites isolating "the CTLA4" ...(see line 8 of the claim). It appears that the intent is to isolate CTLA4 antibodies. Thus, if this is the case, Applicants' are requested to amend the claim as such. Claims 65-72 depend from claim 64.

Claim 65 is unclear. The claim recites that the nucleotide sequence is "included on" the expression vector. It is unclear how this occurs, and thus, renders

the metes and bounds of the claim unclear. Although the sequence can be a part of an expression vector, it is unclear how it is "included".

Claim 68 is unclear, it recites "The antibody of claim 64". However, claim 64 is not directed to an antibody, it is directed to a method of producing an antibody. Appropriate correction is requested.

Claims 69 and 70 recite the "avian cell" of claim 64. Claim 64 only recites an avian oviduct cell, thus, the metes and bounds of these claims are not clear as to if they intend to encompass cells other than the avian oviduct cell claimed. Appropriate correction is requested.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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